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Effects of intrahippocampal injection of ghrelin on spatial memory in PTZ-induced seizures in male rats

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ABSTRACT

Ghrelin (gh) is a peptide hormone that may affect learning and memory. There is some evidence that ghrelin can have antiepileptic effects. So we decided to investigate the possible effects of ghrelin on spatial memory following PTZ-induced seizures in male rats. Ninety male rats were divided into 9 groups including control, saline, ghrelin (0.3, 1.5 or 3 nmol) and pentylenetetrazol (PTZ, 50 mg/kg, i.p.) plus saline or ghrelin (0.3, 1.5 or 3 nmol). All groups were trained in Morris water maze (MWM) for two consecutive days. Our results showed that ghrelin significantly improves spatial memory at the doses of 1.5 or 3 nmol ($P < 0.05$) in normal rats. We also demonstrated the significant impairment of spatial memory in PTZ group ($P < 0.05$). Intrahippocampal injection of ghrelin at the dose of 3 nmol significantly improved spatial memory in PTZ + gh group compared to PTZ group ($P < 0.05$). These findings suggest that ghrelin as a neuropeptide can improve spatial memory in PTZ-treated rats.

1. Introduction

Epilepsy is one of the most prevalent neurological disorders afflicting people of all ages, race and social classes. There are an estimated 50 million people with epilepsy in the world of whom up to 75% live in resource-poor countries with little or no access to medical services or treatment (Broadbent et al., 2004). One of the most common forms of epilepsy is the temporal lobe epilepsy (TLE). Temporal lobe epilepsy often has its onset during childhood and is accompanied with prolonged seizure episodes followed by variable latent periods depending on the severity and frequency of the seizures. The hippocampal system is one of the most epileptogenic regions in the brain (Cendes et al., 1993). The hippocampus has a well-documented role in learning and memory processes particularly in the acquisition of spatial memory and lesions in the CA1 region of hippocampus produce memory deficits and impair spatial memory (Broadbent et al., 2004). Moreover, there is evidence suggesting that epilepsy can be accompanied by memory impairment (Herfurth et al., 2010).

Ghrelin, a 28 amino acid peptide, was identified in the stomach as an endogenous ligand for growth hormone secretagogue receptor (GHSR) in 1999 (Kojima et al., 1999). During fasting, ghrelin is secreted by X/A like cells of stomach (Date et al., 2000), neurons of hypothalamus, pituitary and other tissues (Gualillo et al., 2001; Lu et al., 2001; Cowley et al., 2003; Obay et al., 2007). Ghrelin receptors, which are G protein-coupled receptors (GPCRs), are found in high density in the hypothalamic, hippocampal and pituitary portions of the brain. Nevertheless, a moderate expression has been found in the amygdala, dorsal raphe nucleus and ventral tegmental area (Shuto et al., 2001; Arora, 2006). Ghrelin-containing neuronal cell bodies are localized in the hypothalamic arcuate nucleus, a center that integrates signals for energy homeostasis (Kageyama et al., 2010). Ghrelin increases growth hormone secretion by activating phospholipase C enzyme and increasing intracellular Ca^{2+} level (Wren et al., 2001). This peptide increases the cytosolic Ca^{2+} concentration in NPY-containing neurons isolated from the arcuate nucleus (Kageyama et al., 2012). Ghrelin increases food intake through the enhancement of the expression of agouti-related-peptide (AgRP) and neuropeptide-Y (NPY) in the hypothalamus (Wren et al., 2001). Studies on small-molecule ghrelin receptor agonists (GSK894490A and CP-464709-18) have shown the pro-cognitive role of these receptors on learning and memory (Atcha et al., 2009). Furthermore, there are several evidences that ghrelin increases vagal nerve activity and gives rise to increase in GABA (gamma-aminobutyric acid) and decrease in glutamate secretion (Kamegai et al., 2001; Cowley et al., 2003; Jaszberenyi et al., 2006; Obay et al., 2007). It is also revealed that ghrelin receptor signaling has a pivotal role in development of anticipatory activities that are associated with restricted feeding (Davis et al.,

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